REMARKS

I. Status of the Claims

Claims 26 and 41-54 are pending. No amendment to the claims is made in this response.

II. Rejections under 35 U.S.C. 103(a)

Claims 26 and 41-54 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (U.S. Patent Publication No. 2002/0085997, hereinafter "the Schmidt Application") in view of Sun et al. (Cancer Gene Ther. 2:183-190, 1995, "Sun") and Hiserodt et al. (U.S. Patent No. 6,277,368, issued August 21, 2001, presumptively claiming priority to October 29, 1996, hereinafter "Hiserodt")

Specifically, the Examiner asserts that Schmidt teaches an autologous cell or an allogeneic cell expressing a matching MHC determinant, that Sun teaches an allogeneic IL-2 expressing fibroblast that is transfected with genomic DNA of a tumor cell, and that Hiserodt teaches a tumor vaccine for immunotherapy in human. The Examiner asserts that the claimed invention would have been obvious in view of the combination of the three references. Applicants respectfully traverse the rejection.

1. **The Schmidt Application is not a prior art under any of the provisions 35 U.S.C. §§102(a), 102(b) or 102(e)**

As an initial matter, the published Schmidt Application is not a prior art under any of 35 U.S.C. §§102(a), 102(b) or 102(e). The Schmidt Application was published on July 4, 2002, after the filing date (March 10, 2000) and priority date (January 31, 1997) of the instant application. Thus, the published Schmidt Application is not prior art under either 35 U.S.C. §§102(a) or (b).

Neither is the publication a prior art under 35 U.S.C. §102(e). The Schmidt Application is a National Stage Entry of PCT/EP96/05126, and the PCT was filed November 21, 1996, *i.e.*, prior to November 29, 2000, the effective date of the changes to §102(e) under the American Inventor Protection Act ("the AIPA"). Based on MPEP 706.02(f)(1) I. (C)(3), if the reference results from an international application that has an

international filing date prior to November 29, 2000, the Office is to apply the reference under the provisions of 35 U.S.C. §§102 and 374, prior to the AIPA amendments. Specifically, for U.S. Patent Application publications, the Office is instructed not to apply such references under 35 U.S.C. §102(e). *See* M.P.E.P. 706.02(f)(1) I. (C)(3)(b). Because the Schmidt Application directly results from the International Application that was filed prior to November 29, 2000, the Schmidt Application publication is not qualified as a prior art under 35 U.S.C. §102(e). Thus, the Schmidt Application is not qualified as prior art under any of 35 U.S.C. §§102(a), 102(b) or 102(e).

2. **The remaining references Sun and Hiserodt do not render the claimed invention obvious.**

Further, Applicants submit that the remaining references Sun and Hiserodt, taken alone or in combination, do not render the claimed invention obvious. A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a); *see Graham v. John Deere Co.*, 383 U.S. 1, 14 (1966). The ultimate determination of whether an invention is or is not obvious is based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *See Graham*, 383 U.S. at 17-18.

The obviousness inquiry set forth in *Graham* focuses on whether the prior art as a whole teaches, suggests, or motivates one of ordinary skill in the art to make the invention and whether the skilled artisan would have a reasonable expectation of success in making and using it. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). The suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. The prior art relied upon can be, and usually is, related to the same or similar art as the subject matter of the invention. However, solutions to similar problems from related arts can be used as evidence that the skilled worker would have

appreciated the applicability of said solutions to the problem addressed by the invention. *See KSR International Co. v. Teleflex Inc,* 82 USPQ2d 1385, 1390 (U.S. 2007).

However, the Office should also consider all rebuttal evidence including evidence of secondary considerations, such as commercial success, long felt need, failure of others, and unexpected results, proffered by an applicant. *In re Sullivan*, 84 USPQ2d 1034, 1038 (Fed. Cir. 2007). Evidence of unexpected results can be presented by, for example, showing (1) one of skill in the art could not have combined the claimed element by known method; (2) the elements in combination do not merely perform the function that each element performs separately; or (3) the results of the claimed combination were unexpected. *Examination Guidelines for Determining Obviousness Under 35 USC 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc.* Federal Register, Vol. 72, No. 195, p. 57534. Applicants respectfully contend that a proper application of these rubrics to the instant invention establishes that the pending claims are non-obvious.

a. The Office has not established a prima facie case of obvious based on Sun and Hiserodt.

The claimed invention is directed to a method of treating a tumor in an animal comprising administering to an animal an effective amount of an antigen-presenting cell, wherein the antigen-presenting cell expresses at least one class I MHC or class II MHC determinant that is syngeneic to the animal and at least one class I or class II MHC determinant that is allogeneic to the animal, wherein the antigen-presenting cell is selected from the group consisting of professional antigen-presenting cells and facultative antigen-presenting cells, and wherein the antigen presenting cell is transfected with total genomic DNA isolated from the tumor cells of the animal.

Sun merely relates to a tumor vaccine of allogeneic fibroblasts that express IL-2 and are transfected with genomic DNA of a tumor cell. Sun relates to an allogeneic cell expressing *only* the allogeneic MHC determinants. Sun does not teach or suggest the use of cells that expresses at least one syngeneic *and* one allogeneic MHC determinant.

In fact, Sun *teaches away* from an antigen-presenting cell expressing at least one syngeneic MHC determinant. Sun advocates using allogeneic cells as antigen-presenting

cells for at least two reasons. Sun teaches that immunizing an animal with cells expressing tumor antigens leads to anti-tumor responses only in an *allogeneic* animal but not in a *syngeneic* animal. Additionally, because the allogeneic cells are treated as an allograft, the skilled worker would expect, and Sun teaches, that expression of allogeneic antigens augments the cells' immunogenic properties as a consequence of inducing protection in the recipient against the growth of the modified allogeneic cells (Sun, p.189, right column, 3rd paragraph). Thus, not only Sun fails to teach but in fact *teaches away* from the use of allogeneic cells expressing at least one syngeneic MHC determinant in a tumor vaccine, since syngeneic MHC determinants would be expected to reduce, not enhance, the recipient animal's immunological response.

Hiserodt does not remedy the defect. Hiserodt merely relates to a cellular vaccine and method for using the vaccine in cancer immunotherapy in humans. Hiserodt, however, is completely silent with regard to use of an antigen-presenting cell that expresses both at least one allogeneic MHC determinant and at least one syngeneic MHC determinant on the cell surface (as set forth in Applicants' specification, a semi-allogenic cell). Further, Hiserodt does not teach or suggest an antigen-presenting cell that expresses both at least one allogeneic MHC determinant and at least one syngeneic MHC determinant on the cell surface that is transfected with genomic DNA isolated from tumor cells of the human subject. There is no evidence of record that one of skill in the art would have combined the Sun and Hiserodt references, nor any articulated reason why the skilled worker would have made the combination to achieve the claimed invention. Even if combined, the combination of Sun and Hiserodt would not have provided the skilled worker with every element of the claims. Neither has the Office explained why the differences between the prior art and the claimed invention would have been obvious to one of skill in the art.

b. The claimed invention is not obvious further in view of unexpected results

Further, the claimed invention possesses unexpected properties that are not taught or suggested by the cited art. It was recognized only by Applicants, and set forth only in their instant application, and specifically was not disclosed in any of the cited art, that an antigen presenting cell expressing both an allogeneic and syngeneic MHC determinant

confers superior immunotherapeutic effect compared to cells expressing allogeneic MHC determinants alone. (See p.52, last paragraph of the specification)

The instant application shows surprisingly superior immunostimulatory effects of an antigen presenting cell that expresses both an allogeneic and a syngeneic MHC determinant. For example, the application describes enhanced immunotherapeutic effects using a semi-allogeneic tumor vaccine on mice that were injected with B16 tumor cells at the time of immunization. Figure 3 of the application shows that semi-allogeneic fibroblasts expressing IL-2 and transfected with B16 tumor genomic DNA (LM-IL-$2K^b$/B16) significantly improved the survival of the mice, as compared to mice vaccinated with a control antigen-presenting cell that does not express a syngeneic MHC determinant (LM-IL-2/B16). (Example 6, Figure 3) Similarly, the application also describes an enhanced immunopreventive effect of the semi-allogeneic antigen-presenting cell in mice that were subsequently challenged with B16 tumor cells. Figure 4 shows that mice immunized with semi-allogeneic cells LM-IL-$2K^b$/B16 showed significantly delayed tumor appearance in mice subsequently challenged with B16 tumor cells, as compared to mice immunized with control allogeneic cells LM-IL-2/B16. (Example 6, Figure 4) The unexpectedly superior immunostimulatory effect of a semi-allogeneic cell is disclosed only in Applicants' application, but not recognized or appreciated in the cited art.

In summary, the Sun and Hiserodt references, taken as a whole, do not teach or suggest every claim limitation and would not have rendered the claimed invention obvious to one of skilled in the art. In fact, as demonstrated herein the Sun reference teaches away from using an antigen presenting cell expressing at least one syngeneic MHC determinant and at least one allogeneic MHC determinant. Neither Sun nor Hiserodt, taken alone or in combination, teach or suggest the advantage of a *semi-allogeneic* antigen-presenting cell that expresses both an allogeneic and a syngeneic antigen as tumor vaccine. The superior results of the semi-allogeneic antigen presenting cell as tumor vaccine are completely unexpected in view of Sun or Hiserodt.

Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

III. **Conclusion**

Applicants respectfully submit that all conditions of patentability are met in the pending claims. Allowance of the claims is thereby respectfully solicited.

The Examiner in charge of this application is invited to contact the undersigned representative as indicated below if it is believed to be helpful.

Respectfully submitted,

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